16.1.9 Documentation of Statistical Methods

Documents included:

- Statistical Analysis Plan, Version 1.0, Dated 14 Oct 2022
- Statistical Analysis Modification Requests, Dated 23 Nov 2022
- Statistical Analysis Modification Request, Dated 02 Mar 2023
- Statistical Analysis Plan Amendment 01, Version 1.0, Dated 11 Apr 2023

Parexel International

Cinclus Pharma AG

Protocol #CX842A2201

A randomized double-blind, double dummy, active comparator-controlled dose finding study in patients with erosive esophagitis due to gastro-esophageal reflux disease (GERD) Los Angeles grade C or D, and patients with at least partial symptom response but endoscopically still unhealed after 8 weeks history of standard treatment healing course with proton-pump inhibitor (PPI), to investigate safety, tolerability, and healing rates after 4 weeks treatment of X842 or lansoprazole, and symptom pattern during subsequent 4 weeks treatment with lansoprazole

Statistical Analysis Plan

Version: 1.0

Parexel Project Number: 249403

SPONSOR SIGNATURE PAGE

Approved by: _____ _____

PPD

PPD

Cinclus Pharma AG

Date

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Date

PPD

SDS Life Science AB

Parexel SIGNATURE PAGE

Signatures below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	PPD Project Role: PPD

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
Draft 0.1	26-Oct-2021	New document (without efficacy sections)
Draft 0.2	02-Nov-2021	Updates following internal review + completion of efficacy section (without modelling of primary endpoint)
Draft 0.3	03-Nov-2021	Updates following internal review
Draft 0.4	03-Nov-2021	Updates following client review
Draft 0.5	03-Dec-2021	Updates following internal review (+completion primary endpoint)
Draft 0.6	11 Mar 2022	Updates following client review
Draft 0.7	24 Mar 2022	Updates following client review
Draft 0.8	30 May 2022	Updates following client review
Draft 0.9	16 Jun 2022	Final draft version for dry run
Final 1.0	14 Oct 2022	[List the changes]

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
AESI	Adverse event of special interest
ALAT	Alanine aminotransferase
ALP	Alkaline phosphatase
ASAT	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BID	Twice daily (bis in die)
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
BP	Blood pressure
Bpm	Beats per minute
CI	Confidence interval
C_{max}	Maximum (peak) concentration
CRF/eCRF	Case report form/electronic CRF
CS	Clinically significant
CSP	Clinical Study Protocol
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
DBP	Diastolic blood pressure
DRM	Data Review Meeting
ECG	Electrocardiogram
eGERD	Erosive gastro-esophageal reflux disease
EOS	End-of-study
ET	Early termination
GERD	Gastro-esophageal reflux disease

Abbreviation / Acronym	Definition / Expansion
Hb	Hemoglobin
HBcAg	Hepatitis B core antigen
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
h	hour
ICF	Informed consent form
ICH	International conference on harmonization
IMP	Investigational medicinal product
INR	International normalized ratio
LA grade	The grade of esophagitis according to the Los Angeles classification system
LLOQ	Lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
min	minute
mRESQ-eD	modified Reflux Symptom Questionnaire electronic Diary
N	Number
NA	Not available
NCS	Not clinically significant
o.m.	Every morning
PD	Pharmacodynamic
PK	Pharmacokinetic
PKS	Pharmacokinetic analysis set
PPI	Proton-pump inhibitor
PPS	Per protocol analysis set
PRO/ePRO	Patient reported outcome/electronic PRO

Abbreviation / Acronym	Definition / Expansion
PT	Preferred term
QD	Once daily (quaque die)
QOLRAD	Quality of Life in Reflux and Dyspepsia
QT	The QT interval is measured from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT interval
QTcF	QT corrected using Fridericia's formula
RBC	Red blood cell
s	Second
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SDV	Source data verification
SE	Standard error of the mean
SOC	System organ class
SOP	Standard operating procedures
SUSAR	Suspected unexpected serious adverse reaction
TBL	Total bilirubin
TEAE	Treatment emergent adverse event
WBC	White blood cell
WHO-DD	World Health Organisation - Drug Dictionary

1 INTRODUCTION

Gastro-esophageal reflux disease (GERD) is a common chronic disorder with the prevalence highest in North America and Europe, where at least weekly reflux symptoms range from 10 to 30%.
Linaprazan, the main metabolite of X842, has shown to provide effective acid control in humans.
X842 is developed for the treatment of all patients with erosive esophagitis due to GERD LA grade C or D and of patients with at least partial symptom response but still endoscopically unhealed (LA grades A or B) after at least 8 weeks history of standard treatment healing course with proton-pump inhibitor (PPI).

This is a Phase 2, double-blind study in patients with erosive esophagitis due to GERD Los Angeles (LA) grades C or D, and in patients with at least partial symptom response but still endoscopically unhealed (LA grades A or B) after 8 weeks history of standard treatment healing course with PPI, designed to support dose selection for Phase 3. The pronounced acid control of X842 is assumed to provide high endoscopic healing rates already after 4 weeks treatment course. The four dose levels of X842 are selected based on data from the Phase 1 studies where the 50 mg twice daily (BID) dose displayed an acid control slightly stronger than observed for standard PPI. The dose selection for Phase 3 will be based on the proportion of endoscopic healing following each dose of X842, the respective safety data and the pharmacokinetic (PK) profile. Lansoprazole will serve as an active comparator.

Symptom evaluation during the first 4 weeks will be assessed using the validated patient reported outcome (PRO) QOLRAD (Heartburn version) and patient diaries (mRESQ-eD). Erosive esophagitis due to GERD is known as a chronic disease and the need for maintenance therapy is likely. To further understand the symptom pattern after 4 weeks of powerful gastric acid inhibition all patients undergoing endoscopy at 4 weeks, the end of the blinded phase, will be administered 4 weeks treatment with lansoprazole 30 mg QD. Weekly and daily symptom evaluations will be done during this open-label treatment period to detect symptom pattern and symptom evaluation will be based on telephone interviews and patient diaries. Patients who will terminate the study prematurely will be scheduled for End of Study/Early Termination visit, 4 weeks after cessation of study treatment.
Evaluation of reflux related symptoms and their impact will be assessed by mRESQ-eD, investigator's assessment and QOLRAD.
The study will be conducted in multiple centers in Europe and the US. This will be a randomized, double-blind, active comparator-controlled study with a parallel group design including four arms with X842 and one arm with lansoprazole.

This Statistical Analysis Plan (SAP) describes the planned final analyses for the randomized, double-blind, active comparator-controlled study with a parallel group design including four arms with X842 and one arm with lansoprazole to be included in the Clinical Study Report (CSR).

This SAP is based upon the following study documents:

- Study Protocol, amendment 2.0 (25 February 2022)
- electronic Case Report Form (eCRF) version 2.0 (24 Feb 2022)

2 STUDY OBJECTIVES

Objectives	Endpoints
Primary	
The primary objective of the study is to support dose selection for X842, through assessment of healing of erosive esophagitis due to GERD after 4 weeks of treatment.	Healing of erosive esophagitis due to GERD based on endoscopic assessment after 4 weeks of double-blind treatment.
Secondary	
Evaluate the safety and tolerability of the four dose levels of X842 and lansoprazole, where lansoprazole will serve as the active comparator.	Physical examination, weight, BMI, vital signs, electrocardiogram (ECG) recordings, safety laboratory measurements (hematology/clinical chemistry/urinalysis), adverse event (AE), treatment emergent adverse event (TEAE), adverse event of special interest (AESI), serious adverse event (SAE) reporting, concomitant medication(s).
Evaluate the reflux related symptom pattern during the initial 4 weeks treatment with four dose levels of X842 and with lansoprazole, and the symptom pattern during the subsequent additional 4 weeks (Weeks 5-8) open-label treatment with lansoprazole 30 mg QD.	• Percentage of heartburn-free 24-hour days during the Weeks 1-8 (Visits 2-9) based on eDiary (mRESQ-eD), including splits into day- and nighttime evaluations • Percentage of 24-hour days with at most mild heartburn symptoms during the Weeks 1-8 (Visits 2-9) based on eDiary (mRESQ-eD), including splits into day- and nighttime evaluations • Investigator assessment of symptom at Weeks 1-8 (Visits 2-9) • Reflux related impact as measured by change from baseline in QOLRAD scores assessed after 1, 2, 4 and 8 weeks of treatment.
Exploratory	
[redacted] CCI [redacted]	CCI [redacted]
[redacted] CCI [redacted]	[redacted] CCI [redacted]

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

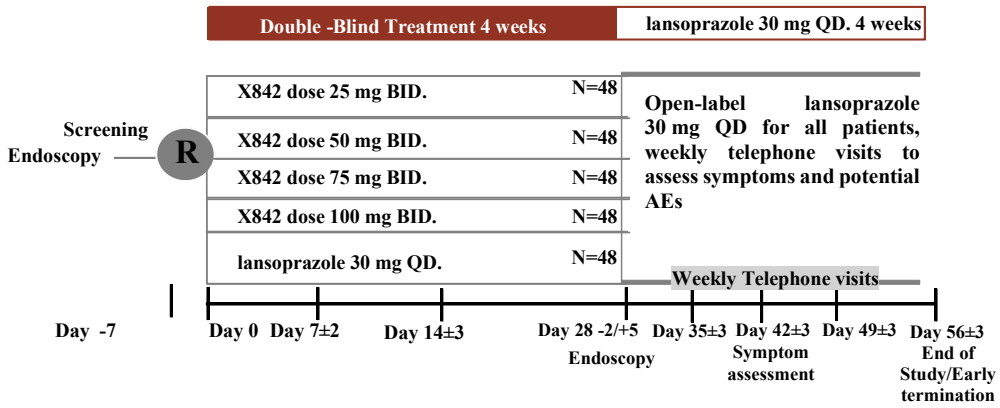
The study will be conducted in multiple centers in Europe and the US.
This is a phase 2, randomized, double-blind, active comparator-controlled study with a parallel group design including four arms with X842 and one arm with lansoprazole.
Approximately 240 patients with erosive esophagitis due to GERD LA grade C or D and patients with erosive esophagitis due to GERD LA grade A or B with at least partial symptom response but still endoscopically unhealed after 8 weeks history of standard treatment healing course with PPI, will be randomized in order to have 200 evaluable patients.
Randomization to one of the treatments with X842 twice daily (BID) 25 mg, 50 mg, 75 mg, 100 mg, or lansoprazole 30 mg once daily (QD) will be based on a 1:1:1:1:1 scheme. One site cannot enroll more than 20% of the overall number of patients (48 patients per site).
The duration of each patient's participation in the study, including screening, blind treatment period and open-label treatment period, will be approximately 60 days.
The patients will be randomized for 4 weeks (28 days, -2/+5 days) of double-blind treatment and will be provided with investigational medicinal product (IMP) for 35 days (including one additional blister pack dispensed at Visit 2/Day 0) to allow for treatment up to the visit window.
Pharmacokinetic (PK) blood sampling pre-dose, close before the first and the second dose administration will be performed at Day 7, Day 14 and Day 28 visits days in all patients.
All patients will have an endoscopic evaluation after 4 weeks treatment. Following the endoscopic evaluation, all patients will receive subsequent 4 weeks of open-label treatment with lansoprazole 30 mg QD. Repeated symptom evaluation to detect symptom pattern will be assessed during this period.

Randomization ratio	TREATMENT GROUP	Morning Capsule	Morning tablet 1	Morning tablet 2	Evening tablet 1	Evening tablet 2
1	X842 (BID) 25 mg	Placebo	25 mg	placebo	25 mg	placebo
1	X842 (BID) 50 mg	Placebo	50 mg	placebo	50 mg	placebo
1	X842 (BID) 75 mg	Placebo	50 mg	25 mg	50 mg	25 mg
1	X842 (BID) 100 mg	Placebo	50 mg	50 mg	50 mg	50 mg
1	Lansoprazole (QD) 30 mg	30 mg	placebo	placebo	placebo	placebo

Four doses of X842 (25 mg, 50 mg, 75 mg, 100 mg, and dummies) will be administered as tablets twice daily. The active comparator lansoprazole 30 mg and its dummy will be administered as capsules once daily in the morning. The study drugs should be taken with 100 mL of noncarbonated water at least 30 minutes prior to meals. The duration of double-blind treatment will be 28 days -2/+5 days. To blind treatment, each patient will receive 2 tablets (containing doses of X842 or its dummy) and one capsule (containing lansoprazole or its dummy) in the morning and 2 tablets (containing doses of X842 or its dummy) in the evening.

The study design is shown below (Figure 1).

Figure 1 Study Design



AE = adverse events; BID = Twice Daily; QD = Once Daily; R = Randomization

The study will comprise 6 visits at the site and 3 telephone visits. Based on the endoscopy findings and/or signed informed consent form (ICF), the screening visit (Visit 1) will take place not more than 7 days prior to randomization and the first dose administration (Visit 2). All patients will then visit the study clinic/investigational site after 7 (Visit 3), 14 (Visit 4) and 28 days (Visit 5) and at the End of Study/Early Termination visit (Visit 9). There are 3 weekly telephone visits after Visit 5. See Table 1 in section 6. All patients who participate in this study and complete Visit 9 (End of Study/Early Termination) are considered to have completed the study (Table 1).

No interim analyses are planned for this study. No data monitoring committees will be used.

3.2 Endpoints and Associated Variables

3.2.1 Efficacy Variables

3.2.1.1 Primary efficacy endpoint

- Healing of erosive esophagitis due to GERD based on endoscopic assessment after 4 weeks of double-blind treatment.

3.2.1.2 Secondary efficacy endpoints

- Percentage of heartburn-free 24-hour days during the Weeks 1-8 based on eDiary (mRESQ-eD).

- Percentage of 24-hour days with at most mild heartburn symptoms during the Weeks 1-8 based on eDiary (mRESQ-eD).
- Investigator assessment of symptom at Weeks 1-8 (Visits 2-9).
- Reflux related impact of symptoms as measured by change from baseline in QOLRAD score assessed after 1, 2, 4 and 8 weeks of treatment.

3.2.1.3 Exploratory efficacy endpoints

CCI

[redacted]

3.2.2 Safety Variables

- Physical examinations: assessment of head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular system, abdomen (including liver and spleen), lymph nodes, genitourinary system (optional) and extremities (musculoskeletal system) after 4 and 8 weeks of treatment.
- Weight and BMI after 4 and 8 weeks of treatment.
- Vital signs: Systolic and diastolic BP, heart rate (pulse), body temperature and respiratory rate after 1, 4 and 8 weeks of treatment.
- 12-lead electrocardiograms (ECG): PQ/PR, QRS, QT and QTcF intervals after 1, 4 and 8 weeks of treatment.
- Clinical laboratory tests: hematology, clinical chemistry, coagulation, and urinalysis parameters after 1, 4 and 8 weeks of treatment.
- Adverse event (AE) assessments: treatment emergent adverse event (TEAE), adverse event of special interest (AESI), serious adverse event (SAE) during the Weeks 1-8 (Visits 2-9).
- Concomitant medication assessments during the Weeks 1-8 (Visits 2-9).

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

'Baseline' is defined as the last available pre-treatment assessment.

'End of Study' is defined as the last available post-treatment assessment.

'Treatment Day' will be calculated relative to the date of randomization i.e. Treatment Day = Assessment Date -Randomization Date + 1.

All data measured on a continuous scale will be presented using summary statistics. Summary statistics is defined as number (N), arithmetic mean, standard deviation (SD), median, minimum, Q1, Q3 and maximum value. Where appropriate 95% confidence intervals will be presented.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n (the number of observations with non-missing values) as the denominator.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Confidence intervals will be presented to one more decimal place than the raw data.

When applicable, summary data will be presented by treatment, and by assessment time. Individual patient data will be listed by patient number, treatment, and, where applicable, by assessment time.

4.3 Software

All report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated environment. For quality control of primary endpoint, R version 4.1.1 will be used.

All report outputs will be provided in Microsoft Word document/PDF format.

4.4 Study Patients

4.4.1 Disposition of Patients

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion.

- A summary of the number of patients screened for entry into the study, the number and percentage of patients excluded prior to randomization by major reason and overall, the total number of randomized patients, the total number of patients randomized and treated, the reasons for not being randomized or treated (Enrolled Set)
- A summary of the number of patients randomized per country and site (Randomized Set)
- A summary of the number of patients randomized and treated (with at least one dose of study medication), treated in DB phase, treated in DB and OL phase and the number and percentage of patients withdrawing from study treatment by study phase together with major reason and withdrawing from the study together with major reason by treatment group and overall (Randomized Set).
- A summary of the number and percentage of patients completing each visit of the study by treatment group and overall (Randomized Set).
- Duration of patient participation in the study (Randomized Set).
- A summary of the Covid-19 impact (at least a visit impacted by the Covid-19 pandemic, visits impacted, type of impact to the visits and relationship to Covid-19 during participation to the study) (Randomized Set).

The duration of patient participation will be calculated in days and derived as:
Duration (days) = Date of last visit or last contact– date of informed consent + 1

By-patient listings will be provided.

- Listing of screen failure patients (Enrolled Set)
- Listing of randomization details (Randomized Set).
- Listing of study treatment discontinuation details (including primary reason and study day at discontinuation, whether treatment was unblinded and the last dose date of study treatment) (Randomized Set).
- Listing of study completion or withdrawal details (including primary reason and study day at discontinuation) (Randomized Set).
- Listing of dates of visit including duration of patient participation and Covid-19 impact (Randomized Set).

4.4.2 Protocol Deviations

All protocol violations will be judged as major or minor, taking composite effects of protocol deviations into consideration.

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. Therefore, patients for whom the clinical outcome is qualitatively affected by the protocol deviations will be excluded.

- Informed consent deviations
- Inclusion/Exclusion criteria deviations
- Disallowed medications
- AEs/SAEs deviations
- IP Administration/ study treatment deviations
- Procedures/tests deviations
- Visit schedule deviations
- Withdrawal criteria deviations

Protocol deviations and any action to be taken regarding the exclusion of patients or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification.

The final classification and effect of each protocol deviation as well as the composite effect of a set of protocol deviations on analysis populations will be assessed prior to the database lock/unblinding on a Blinded Data Review Meeting [BDRM]. Results and population assignments will be summarized in a BDRM report which will be signed off by all relevant scientific experts.

The impact of major protocol deviations on the efficacy and/or safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis set, both including and excluding data potentially affected by major protocol deviations.

The following summaries will be provided:

- A summary of the number and percentage of patients with at least a major protocol deviation and by type of protocol deviation (Randomized Set).

The following listing will be provided:

- All major and minor protocol deviations (Randomized Set).

4.5 Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Population	Description
Enrolled	All patients who signed the ICF (including screening failures).

Population	Description
Randomized	All patients who have been randomized.
Full Analysis Set (FAS)	The full analysis set (FAS) will consist of all patients who have been randomized and received at least 1 dose of IMP. Patients will be analyzed according to randomized treatment (any randomized but not treated patient will be marked and reported as such).
Per Protocol Set (PPS)	The per protocol analysis set (PPS) will consist of all patients who have been randomized and completed the study without any major protocol deviations that are judged to compromise the analysis of the data. Mis-randomized patients will be removed from the PPS. All protocol violations will be judged as major or minor, taking composite effects of protocol deviations into consideration, excluding patients for whom the clinical outcome is qualitatively affected by the protocol deviations.
Safety Analysis Set (SS)	The safety analysis set will consist of all patients who have been randomized and received at least 1 dose of IMP. Patients will be analyzed according to the treatment actually received (in case this differs from randomized treatment).
PK Analysis Set (PKS)	The PK analysis set will consist of all patients who received at least 1 dose of IMP and have at least 1 measurement of plasma concentration of X842/linaprazan. Patients will be analyzed according to the treatment actually received (in case this differs from randomized treatment).

The efficacy summaries and analyses will be based on the **Full Analysis Set,** which is based upon the Intention-to-Treat principle.

For the primary efficacy variable(s), a sensitivity analysis will be performed on the **Per Protocol Set** to assess the robustness of the study conclusions to the choice of analysis population.

Secondary efficacy variable(s) will also be performed on the **Per Protocol Set**.

The PK summaries and analyses will be based on the **PK Analysis Set**.

The safety summaries and analyses will be based on the **Safety Analysis Set**.

Upon database release, protocol deviation and analysis set outputs will be produced and will be sent to Cinclus Pharma for review. An analysis population classification meeting will be arranged to discuss the outputs and to decide which patients and/or patient data will be excluded from certain analysis sets. Decisions made regarding the exclusion of patients and/or patient data from analysis sets will be made prior to unblinding and will be documented and approved by Cinclus Pharma.

The following summary and listing on analysis sets will be provided:

- A summary of the number and percentage of patients in FAS, PPS, Safety Analysis Set and PK Analysis Set by study treatment group and overall and the reason for exclusion from an analysis set (if applicable) (Randomized Set).
- A listing including patient identifier, inclusion/exclusion flag for each analysis set, reason for exclusion from an analysis set (if applicable), randomized and actual study treatment will be provided (Randomized Set).

4.6 Demographics and Baseline Characteristics

The following summary and listing of demographic and baseline characteristics will be based on the FAS:

- A summary of demographic variables: age (years), sex, ethnicity, race, childbearing potential (female only), height (cm), weight (kg), BMI (kg/m^2) and LA grade by study treatment group and overall
- A summary of demographic variables by LA grade by study treatment group and overall
- A summary of viral serology results at baseline
- A summary of H.Pylori results at baseline
- Listing of demographics
- Listing of viral serology and H.Pylori at baseline

Age will be calculated as the number of complete years between a patient's birth date and the date of informed consent.

BMI is calculated automatically in eCRF as [$weight/height^2$] (kg/m^2).

4.7 Medical/Surgical History

Medical/surgical history will be coded by primary system organ class (SOC) and preferred term (PT) using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or higher.
In case of partial or completely missing start date and end date, if this is not possible to decide whether the medical condition is past or current, then it will be considered current.
Smoking history, alcohol consumption history and history intake of drugs and/or anabolic steroids will be presented together with duration of smoking (if former smoker), average number of units of alcohol consumed per week (if current consumption) and time since last drug intake (if former user).

The following summaries will be based on the FAS and provided by study treatment group and overall:

- previous medical conditions or events by MedDRA SOC and PT
- continuing medical conditions by MedDRA SOC and PT
- Smoking history, alcohol consumption history and history intake of drugs and/or anabolic steroids

The following listing will be provided:

- previous or continuing medical conditions or events
- Smoking history, alcohol consumption history and history intake of drugs and/or anabolic steroids

4.8 Prior and concomitant Medications and prior PPI Treatment

Prior and concomitant medications and prior PPI treatment will be coded using the latest available version of the World Health Organization Drug Dictionary (WHO-DD B3) Version March 2020 and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

Medication start and stop dates will be compared to the date of treatment initiation to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only. Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of treatment initiation will be classified as Prior only. If a medication starts before the date of treatment initiation and stops on or after the date of treatment initiation, then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of treatment initiation.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of treatment initiation. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior only. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the date of treatment initiation. In that case, the medication will be assumed to be both Prior and Concomitant.

Where possible, if complete start and end date are available, duration (days) of medications will be calculated and included in listings as duration= end date – start date + 1.

The following summaries will be based on the FAS and provided by study treatment group and overall:

- Prior only medications
- Prior and concomitant medications
- Concomitant only medications
- Prior PPI treatment
- Prior PPI treatment by LA grade
- Newly prior PPI treatment (still on PPI treatment until 28 days prior to treatment initiation)
- Newly prior PPI treatment by LA grade (still on PPI treatment until 28 days prior to treatment initiation)

The following listing will be provided:

- Prior only medications

- Prior and concomitant medications
- Concomitant only medications
- Prior PPI treatment
- Newly prior PPI treatment (still on PPI treatment until 28 days prior to treatment initiation)

4.9 Treatment Exposure / Compliance

4.9.1 Treatment Exposure

Duration of exposure will be expressed in days and calculated for double blind phase, open label phase and overall:

Duration DB (days) = Date of last intake of study treatment in DB phase – date of first intake of study treatment in DB phase + 1
Duration OL (days) = Date of last intake of Lansoprazole in OL phase – date of first intake of Lansoprazole in OL phase + 1
Duration overall (days) = Date of last intake of study treatment – date of first intake of study treatment + 1

The total dose of X842 study drug will be calculated for the DB phase in each treatment group receiving X842, based on the number of tablets of X842 (or dummy) dispensed and returned.
Note that, in the DB phase, patients are supposed to take 4 tablets of X842 (or dummy) per day.

Total dose X842 DB (mg) = (Sum of number of tablets dispensed at start of DB phase - Sum of number of tablets returned at end of DB phase) x Daily dose /Nb of tablets per day

where daily dose is 50 mg, 100 mg, 150 mg or 200 mg depending on the treatment group and Nb of tablets per day is 4 for all treatment groups.

The total dose of Lansoprazole will be calculated for the DB phase (Lansoprazole group only), the open label phase (all treatment groups) and overall (Lansoprazole group only), based on the number of capsules of Lansoprazole (or dummy) dispensed and returned. Note that patients are supposed to take 1 capsule of Lansoprazole (or dummy) per day.

Total dose Lansoprazole DB (mg) = (Sum of number of capsules dispensed at start of DB phase - Sum of number of capsules returned at end of DB phase) x 30.
Total dose Lansoprazole OL (mg) = (Sum of number of capsules dispensed at start of OL phase - Sum of number of capsules returned at end of OL phase) x 30.
Total dose Lansoprazole Overall (mg) = Total dose Lansoprazole DB + Total dose Lansoprazole OL.

The following extent of exposure summaries will be presented on the Safety analysis set by treatment group:

- A Summary of the duration of exposure to treatment, by phase.
- A summary of the total dose of Lansoprazole and X842 by phase.
- Listing of exposure data.

4.9.2 Compliance

Compliance of each treatment group (the 4 X842 treatment groups and the Lansoprazole group) regarding the X842 study drug will be calculated for the DB phase based on the number of tablets of X842 (or dummy) dispensed and returned and on the duration of exposure in days in the DB phase.

Treatment compliance X842 DB (%) = (Sum of number of tablets dispensed at start of DB phase - Sum of number of tablets returned at end of DB phase) / (4 x Duration DB) x 100

Compliance of each treatment group (the four X842 treatment groups and the Lansoprazole group) regarding Lansoprazole study drug will be calculated for each phase based on the number of capsules of Lansoprazole (or dummy) dispensed and returned and on the duration of exposure in days in each phase.

Treatment compliance Lansoprazole DB (%) = (Sum of number of capsules dispensed at start of DB phase - Sum of number of capsules returned at end of DB phase) / (1 x Duration DB) x 100

Treatment compliance Lansoprazole OL (%) = (Sum of number of capsules dispensed at start of OL phase - Sum of number of capsules returned at end of OL phase) / (1 x Duration OL) x 100

Treatment compliance Lansoprazole Overall (%) = (Sum of number of capsules dispensed - Sum of number of capsules returned) / (1 x Duration Overall) x 100

The following compliance summaries will be presented on the FAS by treatment group:

- A summary of the treatment compliance measures by study phase
- A listing of treatment compliance

4.10 Efficacy Evaluation

4.10.1 Analysis and Data Conventions

The primary study objective is to estimate the X842 dose for Phase 3 study with good precision, and hence comparison of different doses of X842 to the active comparator arm (lansoprazole 30 mg) will not

involve any formal statistical testing. Nevertheless, all results for comparator arm will be included in efficacy evaluation summaries.

4.10.1.1 Multi-center Studies

This study is conducted in many sites, and the randomization was not initially stratified by site.
After 128 patients were randomised, a new randomisation scheme with stratification by site was put in place to ease the treatment supply on site. Randomisation was balanced by site to allow the clinical supplies team to better predict the required material types and make them available at each site before a patient is randomised.

For the primary efficacy variable, the statistical models to be used for the estimation of dose-response relationship will adjust for differences between centers, by including 'Center' as a main effects term in the model. Adjustment for center will also be performed, wherever possible, in the analysis of the secondary efficacy variables.

Pooling will be applied to deal with small centers. Countries with less than 20 patients will be grouped. The term 'Center' will be used to define the resulting pseudo-centers, for the summaries and analyses.

Descriptive summaries of primary efficacy variable data by treatment group and center will be provided.

4.10.1.2 Adjustments for Covariates

The primary efficacy analysis will be adjusted for the following baseline covariates:

1. Center
2. Erosive esophagitis due to GERD LA grade C or D, erosive esophagitis due to GERD LA grade A or B who are partial responders to PPI treatment

4.10.1.3 Handling of Dropouts or Missing Data

Primary endpoint:

The number and percentage of patients with missing data for the primary endpoint will be summarized by treatment group, by LA grade, overall and by major reason.

A patient data listing will be provided showing all patients with missing values for the primary endpoint. For these patients, the listing will provide important baseline characteristics, the recorded reason(s) for study discontinuation and the timing of study discontinuation.

In a primary analysis, missing healing results will be replaced with a non-responder approach. If there are more than 5% of patients with missing healing results, a sensitivity analysis will also be performed (tipping point method). Scenarios assuming probability of response 20%, 40%, 60%, 80% and 100% will be simulated. Fifty datasets for each probability will be generated, and for each one, an analysis will be conducted, Rubin rules will be used to combine the results.

Secondary endpoint: QOLRAD

Handling of missing values is described in section 4.10.3.1.

Secondary endpoint: mRESQ-eD

Handling of missing values is described in section 4.10.3.2.

4.10.1.4 Multiple Comparisons/Multiplicity

No formal statistical testing is planned. Hence no adjustments for multiplicity are required.

4.10.1.5 Interim Analyses

No interim analysis.

4.10.1.6 Examination of Subgroups

The uniformity of the treatment effect for the primary efficacy variable will be examined for the following subgroups:

1. Age (<60 years, ≥60 years)
2. Sex (Male, Female)
3. Erosive esophagitis due to GERD LA grade C or D, erosive esophagitis due to GERD LA grade A or B who are partial responders to PPI treatment.

Summaries of the primary efficacy variable by treatment group and subgroup will be produced.

Summaries of the secondary endpoints Percentage of heartburn-free 24-hour days during the Weeks 1-8 based on eDiary (mRESQ-eD) and Percentage of 24-hour days with at most mild heartburn symptoms during the Weeks 1-8 based on eDiary (mRESQ-eD) by treatment group and subgroup will also be produced.

Statistical modeling of dose-response will be performed on subgroups defined by LA grade. No formal statistical analysis will be performed within the other subgroups.

4.10.2 Primary Efficacy Variable(s)

Upper endoscopy for the examination of esophagus will be performed to confirm patient eligibility as well as the primary endpoint. The endoscopy examinations will be recoded on a video shot/digital images and these endoscopy videos/digital images will be evaluated by Investigator or endoscopy specialist, as required. Grade of erosive esophagitis due to GERD will be determined by the appropriately trained Investigator or endoscopist according to the LA classification (see Appendix 8 of protocol).
The endoscopy videos/digital images will be collected into a central database, with the appropriate anonymization. All videos and digital images will be centrally reviewed retrospectively. This review will include reassessment of the LA grading and other findings which may constitute exclusion criterion. The central reading evaluation will override the investigators' evaluations and will be used for all reporting and modelling. In case central reading evaluation is missing for a patient at screening or at week 4, due to poor video quality for example, the investigators' evaluations will replace the missing central reading. Hereafter, analyses based on central reading will consider central readings with imputations of local readings if missing.
Data obtained from patients deemed to have been ineligible for study enrollment following the retrospective analysis will be excluded from the per protocol analysis.
In the FAS analysis, the following subgroups of patients will be evaluated:

- the subgroup of patients classified as erosive with grade A/B or C/D at screening according to central reading
- the subgroup of patients classified as non-erosive (grade 0) at screening according to central reading.

A sensitivity analysis will also be conducted to present the healing results based on investigator or endoscopy specialist assessments (local reading). A second sensitivity analysis will be presented by category of LA Grade as assessed by the investigator and reclassified by central reading.

The primary objective of the study is to support dose selection for X842, through assessment of healing of erosive esophagitis due to GERD based on endoscopic assessment after 4 weeks of treatment. The aim is to identify the dose that will lead to having 85% of the patients have esophageal mucosa healing after 4 weeks of treatment.
Comparison of different doses of X842 to the active comparator arm (lansoprazole 30 mg) will not involve any formal statistical testing.
Lansoprazole treatment group will be analyzed descriptively.

The primary analysis will be performed for both the FAS and PPS as defined in Section 4.5.
In addition, the two subgroups, erosive esophagitis due to GERD LA grade C or D and erosive esophagitis due to GERD LA grade A or B, will be evaluated separately.

In the subgroup of patients with LA grade A or B, some of them were classified as A or B by investigator and thus are partial responders to PPI, but some of them were initially classified as C or D by investigator, and thus may not be partial responders to PPI. A subgroup analysis will be performed on the subgroup of patients with LA grade A/B according to their history of PPI treatment.

The rate of esophageal mucosa healing in the four X842 dose groups after 4 weeks of treatment (endoscopy performed at Visit 5) will be derived using the LA grading of GERD. If the grading is neither A, B, C or D, then the patient will be considered as having esophageal mucosa healing.
The rate of esophageal mucosa healing will be accompanied by 95% Clopper Pearson CI.

The primary analysis will involve dose-response modeling, evaluating a sequence of dose-response models for the healing rate including the Linear, Exponential, E_{max}, Sigmoid E_{max} and Logistic models (on logit scale).
The models will be compared in terms of model fit, and the target dose estimated as the dose providing the target effect of 85% healing rate from the best fitting model will be derived.

Several dose-response models will be fitted with the following factors:

- randomized study treatment (X842 25mg, X842 50mg, X842 75mg and X842 100mg)
- erosive esophagitis due to GERD (LA grade C or D / LA grade A or B)
- Center

Dose-Response Modeling
Multiple Comparison Procedure – Modeling
For all patients assigned to FAS, dose-response modeling will be performed using the multiple comparison procedure – modeling (MCP-Mod) approach [2, 3] with the following models in consideration:

1. Emax: $f(d) = E_0 + E_{max}d/(ED_{50} + d)$.
2. Sigmoidal Emax with $h = 3.5$: $f(d) = E_0 + E_{max}d^{3.5}/({ED_{50}}^{3.5} + d^{3.5})$.
3. Logistic: $f(d) = E_0 + E_{max}/\exp((ED_{50} - d)/\delta)$.
4. Exponential: $f(d) = E_0 + E_1 exp\left(\frac{d}{\delta}\right)$.
5. Linear: $f(d) = E_0 + \beta * d$.

Where:
- d is the dose level,
- ED_{50} the dose that gives 50 percent of the maximum effect,
- h the Hill coefficient,
- δ the rate of change for the logistic and exponential models,
- β is the slope for linear model,
- E_0 the basal effect at $d = 0$ and
- E_1 the scale parameter in the exponential model.

In the MCP-Mod approach, all statistically significant models listed above will be averaged in order to estimate the median dose for a given targeted response via inverse prediction along with associated 95% intervals using a bootstrap re-sampling method.
For the contrast test the following guesstimates will be assumed.

Model	**Guesstimate**
Emax	ED50 = 50
SigEmax1	ED50 = 50
Logistic, Exponential	δ = 200

This MCP-Mod analysis will be performed using the R software ("DoseFinding" and "ggplot2" packages) [5], as follows:

1. MCP step:
    a. Logistic regression model on the response variable with dose levels as categorical to obtain coefficients estimate and the relative covariance matrix.
    b. "Mod" function of the "DoseFinding" package to perform the multiple contrast test (function "MCTtest") part on the pre-specified candidate models
    c. Significant candidate models will be evaluated by t-Test statistic and the adjusted p-value. Candidates for the modeling part will be selected with the following criteria:
        i. Take the most significant candidate model ($p<0.05$) or models if the t-Test statistic is equal.
        ii. Stop if any of the model has not signal ($p>0.05$).

2. Modeling step (Bootstrap):
    a. N = 1,000 bootstrap samples of dose responses will be generated by a multivariate normal distribution with vector mean equal to the logit coefficients estimated on the MCP step and covariance matrix as its coefficients related covariance matrix.
    b. For each Sample:
        i. Fit the model by the "fitMod" function and select the best with goodness of fit based on the AIC criteria.
        ii. Prediction of response probabilities based on the best model.
        iii. Save the predicted values.
3. Compute the median of the bootstrap predicted values and 95% CIs.
4. Extraction of the dose at the target response probability with 95% CI.

Should there be three or more candidate model fail to fit on a bootstrap sample, the estimate for the bootstrap sample will be taken as unreliable. In case less than 70% of bootstrap sample estimates are taken as reliable an additional generalized linear mixed model (GLMM) analysis will be performed as

follows. A regression model with treatment (including Lansoprazole (QD) 30 mg group) and GERD category (with levels of A&B and C&D) as fixed and center as random effect will be fitted to binary data (logistic regression). Number of subjects with evaluable data and least squares mean estimates of response rates with accompanying 90% CIs will be provided for each dose level and for Lansoprazole (QD) 30 mg group using model estimates of the GLM described above.

The following summaries will be provided by study treatment group based on central reading results where some descriptive summaries on FAS will be presented on both subgroups of erosive and non-erosive patients at screening according to central reading. A subgroup analysis based on the LA grade A/B patients by prior PPI treatment will also be presented since some of the LA grade A/B patients were originally LA grade C/D patients as assessed by the investigator.

- Percentage of patients with esophageal mucosa healing after 4 weeks (FAS erosive/non-erosive/PPS)
- Percentage of patients with esophageal mucosa healing after 4 weeks by LA Grade (FAS subgroup of erosive patients/PPS)
- Percentage of patients with esophageal mucosa healing after 4 weeks by age (FAS subgroup of erosive patients /PPS)
- Percentage of patients with esophageal mucosa healing after 4 weeks by sex (FAS subgroup of erosive patients /PPS)
- Percentage of patients with esophageal mucosa healing after 4 weeks by center (FAS subgroup of erosive patients /PPS)
- Percentage of patients with esophageal mucosa healing after 4 weeks by H.Pylori at Baseline (FAS erosive/non erosive /PPS)
- Percentage of patients with esophageal mucosa healing after 4 weeks by Prior PPI Treatment (FAS Patients with LA Grade A/B)
- Bar-charts of percentage of patients with esophageal mucosa healing after 4 weeks (FAS erosive/non erosive /PPS)
- Bar-charts of percentage of patients with esophageal mucosa healing after 4 weeks by LA Grade (FAS subgroup of erosive patients /PPS)
- MCP-MOD: Testing a dose-response signal for Response Rate (FAS subgroup of erosive patients /PPS)
- Figure for dose-response shapes based on model-averaging method over all models in the candidate set (FAS subgroup of erosive patients /PPS)
- Results of the contrast test from the MCP-Mod analysis (FAS subgroup of erosive patients /PPS)
- Model parameter estimates of the individual dose-response models (FAS subgroup of erosive patients /PPS)

- Estimation of potential target dose based on model-averaging method over all models in the candidate set (FAS subgroup of erosive patients /PPS)

A sensitivity analysis based on local readings will be provided by study treatment group:

- Percentage of patients with esophageal mucosa healing after 4 weeks (Investigator or Endoscopy specialist reading) (FAS)
- Percentage of patients with esophageal mucosa healing after 4 weeks by LA Grade (Investigator or Endoscopy specialist reading) (FAS)

A second sensitivity analysis based on local readings and how those local readings were reclassified by central reading will be provided by study treatment group.

There will be 6 categories:

- Grade C/D that stayed C/D
- Grade C/D reclassified as A/B
- Grade C/D reclassified as grade 0 (non erosive) – if any
- Grade A/B reclassified as C/D – if any
- Grade A/B that stayed A/B
- Grade A/B reclassified as grade 0 (non erosive)

- Percentage of patients with esophageal mucosa healing after 4 weeks by Investigator LA Grade and its reclassification (FAS)

A listing of upper endoscopy results will be provided.

4.10.3 Secondary Efficacy Variables

Analyses of the secondary efficacy endpoints will be performed for the FAS and the PP as defined in Section 4.5.

QOLRAD scores and mRESQ-eD means or proportions will be estimated using a Generalized Linear Mixed Model (GLMM) approach using information of each week for each subject, on observed data, assuming missing at random.

The models will be implemented using all available timepoints (as categorical), the X842 dose level or lansoprazole as covariate and the related interaction, center and erosive esophagitis due to GERD (LA grade C or D / LA grade A or B.

Toeplitz covariance matrix will be assumed. In case of convergence failure, the following matrices will be tested until convergence is reached: 1. Compound Symmetry, 2. Autoregressive 1 (AR-1).
Mean and standard error estimated from the model will be provided in the outputs. Median, Q1, Q3, Min and Max will be reported as observed data.

4.10.3.1 QOLRAD

Reflux related impact will be assessed based on the patient reported outcome (PRO) QOLRAD. The heartburn version of the QOLRAD is a disease specific instrument and contains 25 questions addressing concerns associated with gastrointestinal symptoms. Each question is scored from 1 to 7, where a higher score represents a higher (“better”) health-related quality of life.

The QOLRAD will be completed pre-dose by patients at Visits 2 (Baseline), 3 (Week 1), 4 (Week 2), 5 (Week 4), and 9 (Week 8) (see Table 1 in section 6.1).

The questions are categorized into five domains: emotional distress (six questions), sleep disturbance (five questions), vitality (three questions), food/drink problems (six questions) and physical/social functioning (five questions).

- Emotional distress (questions 12, 14, 15, 17, 19, 22)
- Sleep disturbance (questions 8, 10, 11, 18, 21)
- Food/drink problems (questions 3, 5, 9, 13, 16, 20)
- Physical/social functioning (questions 2, 6, 23, 24, 25)
- Vitality (questions 1, 4, 7)

For the calculation of domain scores, in case of missing items, these missing items can be replaced under specific conditions (the half-scale method) as follows:

- If 50% or more of the questions in one dimension are completed, the mean value of the completed items should replace the missing responses.

- If less than 50% of the questions in one dimension are completed, the missing responses will not be replaced.

The score in each domain will be calculated as the mean of all items in that domain, only if all items are not missing after replacement.

To evaluate the reflux related impact pattern during the initial 4 weeks treatment and the subsequent additional 4 weeks (Weeks 5-8) open-label treatment with lansoprazole 30 mg QD, the following summaries will be provided by study treatment group and assessment day:

- A summary of QOLRAD domain scores and change from baseline (FAS/PP)
- A plot of QOLRAD domain scores at baseline and Week 1, Week 2, Week 4 and Week 8 (FAS/PP).

A listing of QOLRAD results will be provided. Original values and imputed values will be provided, together with domain scores.

4.10.3.2 mRESQ-eD

Reflux related symptoms will also be assessed based on the modified RESQ-eDiary. mRESQ-eD contains 8 items where 5 items assess severity (Did not have – Severe) and 3 items assess frequency (Never – Very often) of symptoms.

- Heartburn domain (questions 1, 2) assess severity (0=Did not have, 1=Very mild, 2=Mild, 3=Moderate, 4=Moderately severe, 5=Severe).
- Regurgitation domain (questions 6, 7, 8) assess frequency of symptoms (0=Never, 1=Rarely, 2=Sometimes, 3=Often, 4=Very often).
- Difficulty swallowing (question 3) assess severity of symptoms (0=Did not have, 1=Very mild, 2=Mild, 3=Moderate, 4=Moderately severe, 5=Severe).
- Hoarseness (question 4) assess severity of symptoms (0=Did not have, 1=Very mild, 2=Mild, 3=Moderate, 4=Moderately severe, 5=Severe).
- Cough (question 5) assess severity of symptoms (0=Did not have, 1=Very mild, 2=Mild, 3=Moderate, 4=Moderately severe, 5=Severe).

Patients will be asked to report their symptoms every 12-hours, once before the morning dose and once before the evening dose of the IMP through week 1 to week 8.

Missing values will be imputed if possible.

Imputation of missing values:

For each item, morning recordings will be regarded as one sequence of observations and evening recordings as another sequence of observations. Missing values in the sequence of morning or evening recordings respectively will be imputed according to the following rules:

- If a single observation is missing, the missing value will be replaced by the larger of the two surrounding values.
- If two or more consecutive observations are missing the values will remain missing.

Item values of severity or frequency for a day (approximately a 24 h period) will then be constructed using the imputed sequences of evening and morning recordings of severities or frequencies. A day will consist of the morning and evening recording of each day starting on Day 1, the day after the first treatment intake. All recordings taken on the day of first treatment intake will be considered as Day 0 recordings. There could be some pre-dose recordings and some post-dose recordings depending on the time the patient had the first dose.

- The daily item severity or frequency will be defined as the maximum of the two recordings.
- If either the morning or the evening recording is missing, the daily value will be set to the available value.
- If both morning and evening recordings are missing, the daily value will be set to missing.

Baseline morning, evening and 24-hour daily recording will be defined using the recordings prior to the first treatment dose, if these recordings are available.

Domain scores:

The domain severity or frequency on a given day, morning or evening will be derived as the highest severity or frequency of the items that form the domain. If some items are missing, the highest value will be chosen amongst available items.

Heartburn domain:

- Morning score: the highest severity score between item 1 and item 2 of the morning assessment (min-max 0-5).
- Evening score: the highest severity score between item 1 and item 2 of the evening assessment (min-max 0-5)
- Daily score: the highest severity score between daily assessments of item 1 and item 2 (min-max 0-5)

Regurgitation domain scores are constructed in the same way as Heartburn domain using the items that form the domains.

Weekly means of the daily scores, of the morning scores and of the evening scores will then be calculated and presented by week for each domain or item. A minimum of 4 days during a week with severity or frequency of symptoms recorded is required to calculate weekly means for all the 3 domains.

Heartburn free:

Heartburn-free in a 24-hour day is defined as a daily score of 0 for the heartburn domain, and the number of heartburn-free days over a week will be calculated. The percentage of heartburn-free days for a patient over a week will be calculated as:
% heartburn-free days = number of days with daily score =0 / number of days the severity of symptom is recorded x 100.
A minimum of 4 days during a week with severity of symptoms recorded is required, otherwise, the percentage will be set as missing for that week.
The percentage of heartburn-free in the morning and heartburn-free in the evening will also be calculated for morning and evening records respectively.

Heartburn with at most mild symptoms:
Heartburn with at most mild symptoms (either no symptoms, very mild symptoms or mild symptoms) in a 24-hour day is defined as all the items in the domain that have a daily score of maximum 2, and percentage of heartburn- at most mild symptoms days for a patient over a week will be calculated as:
% heartburn-at most mild symptoms days = number of days where all items have daily score ≤ 2 / number of days the severity of symptom is recorded x 100.
A minimum of 4 days during a week with frequency of symptoms recorded is required, otherwise, the percentage will be set as missing for that week.
The percentage of heartburn-at most mild symptoms in the morning and heartburn-at most mild symptoms in the evening will also be calculated for morning and evening records respectively.

The following summaries will be provided by study treatment group and assessment time (morning, evening or daily):

- mRESQ-eD: Summary of weekly mean domain scores/items during the Weeks 1-8 (FAS/PP)
- A plot of weekly mean domain scores/items during the Weeks 1-8 (FAS/PP)
- mRESQ-eD: Percentage of heartburn-free 24-hour days during the Weeks 1-8 (FAS/PP)
- mRESQ-eD: Percentage of heartburn-at most mild symptoms 24-hour days during the Weeks 1-8 (FAS/PP)
- A plot of heartburn-free rate from 1 to 8 weeks of treatment (FAS/PP)
- A plot of heartburn- at most mild symptoms rate from 1 to 8 weeks of treatment (FAS/PP)

Listings of mRESQ-eD results will be provided. Item scores, domain scores and weekly mean domain scores will be provided (morning, evening and daily scores).

4.10.3.3 Heartburn assessed by investigator

At each visit, Investigator will assess the severity of patients' heartburn, regurgitation and dysphagia in the 7 days prior to the visit. The assessment will include both the severity grade and the frequency of symptoms.

The potential frequency is defined as one of these grades: All of the time, Most of the time, Quite a lot of the time, Some of the time, A little of the time, Hardly any of the time and None of the time. Symptoms are scored as either none, mild, moderate or severe.

The following summaries will be provided by study treatment group and visit:

- A summary of investigator assessment of symptoms (severity and frequency of heartburn, regurgitation and dysphagia) at Weeks 1-8 (Visits 2-9) (FAS/PP)
- A bar chart of investigator assessment of heartburn (severity and frequency) at baseline and from 1 to 8 weeks of treatment (FAS/PP)
- A bar chart of investigator assessment of regurgitation (severity and frequency) at baseline and from 1 to 8 weeks of treatment (FAS/PP)
- A bar chart of investigator assessment of dysphagia (severity and frequency) at baseline and from 1 to 8 weeks of treatment (FAS/PP)

A listing of investigator assessment of symptom at Weeks 1-8 (Visits 2-9) will be provided:

4.10.4 Exploratory efficacy endpoint

CCI [redacted]

CCI [redacted]

Pre-dose plasma concentrations will be collected twice daily, pre-dose, before the first and the second dose administration at Day 7, Day 14 and Day 28 visits in all patients.

The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: n, arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric CV%, median, minimum and maximum values.

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

4.11 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Set as defined in Section 4.5.

4.11.1 Adverse Events

An AE is any untoward medical occurrence in a clinical study patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including clinically significant abnormal values from relevant tests, such as clinical safety laboratory tests, ECGs, vital signs), symptom, or disease temporally associated with the use of an IMP, regardless of whether it is considered related to the IMP.
Collection of AEs will start directly after the ICF has been signed. Only AEs related to study procedure will be collected between screening visit and the first IMP administration.

A TEAE is any AE only present after the initiation of IMP administration or any event already present that worsens in either severity or frequency following exposure to the IMP and on or before 30 days after the date of last dose of study treatment.

Where dates are missing or partially missing, adverse events will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event started prior to the first dose of study treatment or more than 30 days after the last dose of study treatment.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher for System Organ Class (SOC) and Preferred Term (PT).

AEs are divided into defined severity grades (Grade 1: mild, Grade 2: moderate, Grade 3: severe, Grade 4: life-threatening and Grade 5: death).

AEs are also divided into 3 different causal relationships (Probable, Possible and Unlikely). An AE is considered causally related to the use of the IMP when the causality assessment is probable or possible.

The following summaries will be provided by treatment group and overall.

- An overview table summarizing the number and percentage of patients with at least one of the following AEs together with the corresponding number of events for each of these AE categories listed below:
  - any AE,
  - any TEAE,
  - any severe TEAE,
  - any treatment related TEAE (ADR),
  - TEAE leading to discontinuation from the study,
  - Any Serious Adverse Event (SAE).
  - Any treatment emergent SAE,
  - Any treatment emergent adverse event of special interest (AESI)
- A summary of the number and percentage of patients reporting a TEAE by SOC and PT,
- A summary of the number and percentage of patients reporting a TEAE by PT by frequency of occurrence,
- A summary of the number and percentage of patients reporting a TEAE by severity, SOC and PT,
- A summary of the number and percentage of patients reporting a TEAE by causality to study treatment, SOC and PT,

All adverse event summaries will provide the number of patients reporting at least one adverse event and the total number of events reported and will be ordered alphabetically for SOC and PT within SOC.

In summary by frequency of occurrence, the preferred terms will be ordered according to the frequency of occurrence in the total column.

AEs will be counted as follows:

- In summaries of number of patients experiencing AEs, patients with more than one AE within a particular SOC are counted only once for that SOC. Similarly, patients with more than one AE within a particular PT are counted only once for that PT.
- In summaries of number of patients experiencing AEs, patients reporting a TEAE more than once within that SOC/ PT, but with different severities, the worst severity will be used in the corresponding severity summaries.

- In summaries of number of patients experiencing AEs, patients reporting a TEAE more than once within that SOC/ PT, but with different relationships, the worst relationship will be used in the corresponding relationship summaries.
- If the severity is missing for a TEAE, it will be considered as missing in the summary tables.
- If the causality is missing for a TEAE, it will be considered as missing in the summary tables.

In addition, a listing with all AEs data will be listed by treatment including non-TEAEs. Treatment-emergence status will be flagged in the listing.

AE duration will be derived with the formula:
AE duration = (AE end date - AE onset date + 1); in case of AE ongoing, the date of last contact with the patient will be used as AE end date for the scope of deriving the AE duration.

A by-patient listing of all AEs (including non-treatment-emergent events: flagged) will be provided. These listings will be presented by treatment group and will include: patient identifier, age, sex, AE (SOC, PT, and verbatim term), date of onset, date of resolution or ongoing, duration, severity, NCI CTCAE toxicity grade, seriousness, causality to study treatment, causality to non-study treatment, action taken and outcome.

4.11.2 Adverse Events of Special Interest (AESI)

The following conditions should be considered AEs of special interest:

a. ALT or AST ≥ 8 x ULN
b. ALT or AST ≥ 5 x ULN for 2 or more weeks
c. ALT or AST ≥ 3 x ULN **and** total bilirubin ≥ 2 x ULN (or ALT or AST ≥ 3 x ULN **and** INR > 1.5)
d. ALT or AST ≥ 3 x ULN accompanied by clinical symptoms believed to be related to hepatitis or hypersensitivity, such as new or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash
e. ALT or AST ≥ 5 x ULN but < 8 x ULN and cannot be monitored at least weekly for ≥ 2 week

Hy's Law, defined as ≥ 3 x ULN ALT or AST **with coexisting** ≥ 2 x ULN total bilirubin with no alternative explanation for the biochemical abnormality other than IMP (for example elevated ALP indicating cholestasis, viral hepatitis, other medication) must always be reported without delay as an AESI, and, if applicable, also as an SAE.

All potential AESIs will be medically evaluated during the study, before the database lock and unblinding, by the sponsor to identify events which could possibly be AESIs.

A list of PTs for AESIs will be provided for identification and AESIs will be flagged in the database.

The following summary and listing will be provided.

- A summary of the number and percentage of patients reporting an AESIs by SOC and PT.
- Listing of AESIs

4.11.3 Deaths, Serious Adverse Events, and Other Significant Adverse Events

The following summaries will be provided by treatment group and overall.

- A summary of the number and percentage of deaths (including SAEs with fatal outcome and deaths as PT),
- A summary of the number and percentage of patients reporting a serious TEAE, by SOC and PT,
- A summary of the number and percentage of patients with TEAEs leading to discontinuation of study treatment, by SOC and PT.

The following listings will be provided:

- A listing of all deaths that occurred during the study,
- A listing of all SAEs,
- A listing of all AEs leading to discontinuation of study treatment.

4.11.4 Clinical Laboratory Evaluation

The following laboratory parameters of hematology, blood chemistry, coagulation and urinalysis will be assessed at screening, Visit 3 (Day 7), Visit 5 (Days 28) and Visit 9 (EOS):

Hematology: Hematocrit, Hemoglobin (Hb), Platelet count, Red blood cell (RBC) count and White blood cell (WBC) count with differential count.

Blood chemistry: Alanine aminotransferase (ALAT), Alkaline phosphatase (ALP), Albumin, Aspartate aminotransferase (ASAT), Bilirubin (total and conjugated), Calcium, Chloride, Creatinine, Gamma-glutamyl transferase (GGT), Magnesium, Phosphorous, Potassium, Sodium, Urea nitrogen, Uric acid and Gastrin.

Coagulation: International Normalized Ratio.

Urinalysis (dip stick): Glucose, Hemoglobin/erythrocytes, Nitrite, Protein, Specific gravity, pH and Ketones.

Urine Drug Screen: Amphetamine, Barbiturate, Cannabinoid, Cocaïne, Benzodiazepine and Opiate.

Serum Gastrin

Laboratory test results for hematology, chemistry, and coagulation parameters will be classified as normal or abnormal (high or low) according to the applicable laboratory's normal ranges.

For by-visit summaries, the last non-missing assessment (including repeat assessments) recorded at each visit will be summarized. Baseline is defined as the last assessment prior to study drug intake and will be the screening assessment.

The following summaries will be based on the Safety Analysis Set.
Summaries for actual values and change from baseline will be presented by treatment group and assessment day for each study site separately (due to assays performed locally). Summaries for categorical values of normality/abnormality will be presented by treatment group and assessment day.

- Hematology and coagulation: laboratory test value and change from baseline by visit
- Hematology and coagulation: laboratory test value and change from baseline by visit in patients with LA grade A/B
- Hematology and coagulation: laboratory test value and change from baseline by visit in patients with LA grade C/D
- Hematology and coagulation: number and percentage of patients experiencing low, normal or high laboratory test result
- Hematology and coagulation: number and percentage of patients experiencing low, normal or high laboratory test result in patients with LA grade A/B
- Hematology and coagulation: number and percentage of patients experiencing low, normal or high laboratory test result in patients with LA grade C/D
- Chemistry: laboratory test value and change from baseline by visit
- Chemistry: laboratory test value and change from baseline by visit in patients with LA grade A/B
- Chemistry: laboratory test value and change from baseline by visit in patients with LA grade C/D
- Chemistry: number and percentage of patients experiencing low, normal or high laboratory test result
- Chemistry: number and percentage of patients experiencing low, normal or high laboratory test result in patients with LA grade A/B
- Chemistry: number and percentage of patients experiencing low, normal or high laboratory test result in patients with LA grade C/D
- Urinalysis: laboratory test category (normal, abnormal not clinically significant or abnormal clinically significant) and toxicity grade by visit
- Urinalysis: laboratory test category (normal, abnormal not clinically significant or abnormal clinically significant) and toxicity grade by visit in patients with LA grade A/B
- Urinalysis: laboratory test category (normal, abnormal not clinically significant or abnormal clinically significant) and toxicity grade by visit in patients with LA grade C/D
- Serum Gastrin: laboratory test value and change from baseline by visit

- Serum Gastrin: laboratory test value and change from baseline by visit in patients with LA grade A/B
- Serum Gastrin: laboratory test value and change from baseline by visit in patients with LA grade C/D

Laboratory values (hematology, chemistry, coagulation and urinalysis) will be listed by patient and study time point including changes from baseline (with the exception of urinalysis).

All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings.

The following listings of laboratory parameters will be provided:

- Hematology and coagulation parameters
- Chemistry parameters
- Urinalysis

4.11.5 Vital Signs

The following vital signs measurements will be assessed at screening, Visit 3 (Day 7), Visit 5 (Days 28) and Visit 9 (EOS):

- Systolic blood pressure (SBP) [mmHg].
- Diastolic blood pressure (DBP) [mmHg].
- Heart rate (bpm).
- Body temperature (oral) [°C].
- Respiratory rate (breaths/per minute)

Systolic blood pressure, diastolic blood pressure and heart rate will be classified as normal or abnormal

For by-visit summaries, the last non-missing assessment (including repeat assessments) recorded at each visit will be summarized. Baseline is defined as the last assessment prior to study drug intake and will be the screening assessment.

The following summaries will be based on the Safety Analysis Set and provided by study treatment group and assessment day:

- A summary of vital signs and change from baseline
- Vital signs: number and percentage of patients with normal or abnormal values

A listing of vital signs results will be provided.

4.11.6 Resting 12-lead Electrocardiograms

Single 12-lead ECG will be recorded at screening, Visit 3 (Day 7), Visit 5 (Days 28) and Visit 9 (EOS) and the following parameters will be obtained:

- Heart rate (bpm)
- PR interval
- QRS complex (msec)
- QT interval (msec)
- QTcF interval (msec)
- PR segment
- ST segment

The ECG will be evaluated by the Investigator as 'Normal', 'Abnormal, non-clinically significant (NCS)' or 'Abnormal, clinically significant (CS)'.

Baseline is defined as the last assessment prior to study drug intake and will be the screening assessment.

The following summaries will be based on the Safety Analysis Set and provided by study treatment group and assessment day:

- A summary of 12-lead ECG and change from baseline
- 12-lead ECG: number and percentage of patients with normal, abnormal NCS and abnormal CS values

A listing of 12-lead ECG results will be provided.

4.11.7 Physical examination

A complete physical examination will be performed at screening, Visit 5 (Days 28) and Visit 9 (EOS) and will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular system, abdomen (including liver and spleen), lymph nodes, genitourinary system (optional) and extremities (musculoskeletal system).

The following summaries will be based on the Safety Analysis Set and provided by study treatment group and assessment day:

- Physical examination: number and percentage of patients with abnormal findings by physical site

A listing of physical examination will be provided.

4.11.8 Weight and BMI

Weight will be measured at screening, Visit 5 (Days 28) and Visit 9 (EOS).

Body mass index (BMI) will be calculated from the height in meter and weight in kg recorded and rounded off to the nearest whole number.

BMI = [weight/height^2] (kg/m^2).

Baseline is defined as the last assessment prior to study drug intake and will be the screening assessment. Absolute and relative change from baseline will be calculated as follows:

- Absolute change at Visit x= weight at Visit x – weight at baseline
- Relative change at Visit x= (weight at Visit x – weight at baseline) / weight at baseline

The following summaries will be based on the Safety Analysis Set and provided by study treatment group and assessment day:

- A summary of Weight with absolute and relative change from baseline
- A summary of BMI with absolute and relative change from baseline

Weight and BMI will be listed together with vital signs.

4.11.9 Safety Monitoring (Independent Data Monitoring Committee [IDMC], Data Monitoring Committee [DMC], Data and Safety Monitoring Board [DSMB])

Not applicable

4.12 Determination of Sample Size

[redacted]
CCI

[redacted]

CCI

[redacted]

4.13 Changes in the Conduct of the Study or Planned Analysis

Protocol amendments don't have statistical implication.

Results of upper endoscopy from investigator or endoscopy specialist will not be simply overridden by central reading. The records will be kept and described (LA grade and healing response) and the concordance with central reading will be investigated.

Descriptive table of the investigator or endoscopy specialist's results will be prepared, as well as a concordance table of the investigator or endoscopy specialist and central reading results.

5 REFERENCES

[1] SAS® Version 9.4 of the SAS System for Personal Computers. Copyright ©□2020. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

[2] Bretz, Frank, José C. Pinheiro, and Michael Branson. "Combining multiple comparisons and modeling techniques in dose‐response studies." Biometrics 61, no. 3 (2005): 738-748.

[3] Pinheiro, José, Björn Bornkamp, Ekkehard Glimm, and Frank Bretz. "Model‐based dose finding under model uncertainty using general parametric models." Statistics in medicine 33, no. 10 (2014): 1646-1661.

[4] R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

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6 APPENDICES

6.1 Schedule of Assessments

Table 1 Overall Schedule of Assessments

Visit	Visit 1 Screening	Visit 2	Visit 3	Visit 4	Visit 5	Tel Visit 6	Tel Visit 7	Tel Visit 8	Visit 9 End of Study / Early Termination
Assessment/Study day	**Day -7[14] to Day 0**	**Day 0**	**Day 7 ±2 days**	**Day 14 ±3 days**	**Day 28 -2/+5 days**	**Day 35 ±3 days**	**Day 42 ±3 days**	**Day 49 ±3 days**	**Day 56 ±3 days**
Assessment/Study week		**Randomization**	**Week 1**	**Week 2**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**
	Screening Period	**Blinded Treatment Phase**				**Open-Label Phase**			
Informed consent	X								
Demographics	X								
Inclusion/exclusion criteria	X	X							
Medical/surgical history [1]	X								
Weight, height [2]	X				X				X
Complete physical examination	X				X				X
Drugs of abuse	X								X

Visit	Visit 1 Screening	Visit 2	Visit 3	Visit 4	Visit 5	Tel Visit 6	Tel Visit 7	Tel Visit 8	Visit 9 End of Study / Early Termination
Assessment/Study day	**Day -7[14] to Day 0**	**Day 0**	**Day 7 ±2 days**	**Day 14 ±3 days**	**Day 28 -2/+5 days**	**Day 35 ±3 days**	**Day 42 ±3 days**	**Day 49 ±3 days**	**Day 56 ±3 days**
Assessment/Study week		**Randomization**	**Week 1**	**Week 2**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**
	Screening Period	**Blinded Treatment Phase**				**Open-Label Phase**			
Viral serology testing [3]	X								
Vital signs [4]	X		X		X				X
12-lead ECG evaluation	X		X		X				X
Safety laboratory [5]	X		X		X				X
H. pylori testing [6]	X								
Pregnancy test [7]	X				X				X
Randomization		X							
Patients provided with study drugs for blinded phase		X	X	X					

Visit	Visit 1 Screening	Visit 2	Visit 3	Visit 4	Visit 5	Tel Visit 6	Tel Visit 7	Tel Visit 8	Visit 9 End of Study / Early Termination
Assessment/Study day	**Day -7[14] to Day 0**	**Day 0**	**Day 7 ±2 days**	**Day 14 ±3 days**	**Day 28 -2/+5 days**	**Day 35 ±3 days**	**Day 42 ±3 days**	**Day 49 ±3 days**	**Day 56 ±3 days**
Assessment/Study week		**Randomization**	**Week 1**	**Week 2**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**
	Screening Period	**Blinded Treatment Phase**				**Open-Label Phase**			
Patients provided with Lansoprazole 30 mg for open-label phase					X				
PK blood sampling [8]			X	X	X				
Upper endoscopy	X[15]				X				
Symptom evaluation using QOLRAD Heartburn [9]		X	X	X	X				X
Daily symptom diary (mRESQ-eD) completion by patient		X	X	X	X	X	X	X	X
Symptom diary provision/training/ review[10]		X	X	X	X	X	X	X	X

Visit	Visit 1 Screening	Visit 2	Visit 3	Visit 4	Visit 5	Tel Visit 6	Tel Visit 7	Tel Visit 8	Visit 9 End of Study / Early Termination
Assessment/Study day	**Day -7[14] to Day 0**	**Day 0**	**Day 7 ±2 days**	**Day 14 ±3 days**	**Day 28 -2/+5 days**	**Day 35 ±3 days**	**Day 42 ±3 days**	**Day 49 ±3 days**	**Day 56 ±3 days**
Assessment/Study week		**Randomization**	**Week 1**	**Week 2**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**
	Screening Period	**Blinded Treatment Phase**				**Open-Label Phase**			
Symptom assessment by Investigator [11]	X	X	X	X	X	X	X	X	X
AE reporting [12]	X	X	X	X	X	X	X	X	X
Prior/concomitant medications [13]	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; ECG, electrocardiogram; ICF, informed consent form; LA, Los Angeles; PK, pharmacokinetic.

1. Including smoking (current status), alcohol consumption, and intake of drug of abuse.
2. Height only at screening
3. Human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis B core antigen (anti-HBcAg), antibody to hepatitis C virus (anti-HCV) testing at central and/or local laboratory. Patient should discontinue the study if result from central laboratory is positive.
4. Systolic and diastolic blood pressure (BP) [mmHg], heart rate [beats per minute], body temperature and respiratory rate [per minute].
5. Hematology, blood chemistry, coagulation (central laboratory), urinalysis (at site). Serum gastrin at screening and at Visit 5 (central laboratory).
6. *H. pylori* will be analyzed in central laboratory from serum and the result will not be needed for randomization.
7. Women of childbearing potential only. Serum pregnancy test at central laboratory at screening and urine pregnancy test at clinic/investigational site prior to the dose administration at Visit 5, and at End of Study / Early Termination.

8. PK measured in all patients just before the first and the second dose on the day of the visit. At all PK sampling occasions, the time since latest study drug administration must be noted in the case report form (CRF). Pharmacokinetic samples will be collected 12 hours after the previous study drug dose administration or as close to this timepoint as possible, however, still pre-dose.
9. QOLRAD assessment must be done pre-dose. QOLRAD will be completed by patients during site visits at Visit 2, 3, 4, 5 and 9.
10. Patients will be trained on how to complete the symptoms diary during Visit 2 and the actual diary will be provided at Visit 2.
11. At each visit, Investigator should assess the severity of patients' heartburn, regurgitation and dysphagia in the 7 days prior to the visit. The assessment will include both the severity grade and the frequency of symptoms. Symptoms are scored as follows: none (no complaints), mild (aware of symptom, but easily tolerated), moderate (discomforting symptom, sufficient to cause interference with normal daily activities and/or sleep), severe (incapacitating symptom, with inability to perform normal daily activities and/or sleep)
12. Collection of AEs will start directly after the informed consent form (ICF) has been signed. During the screening period, only AEs related to study procedure will be reported.
13. For definitions of prior and concomitant medication, see Section 8.1.6 of protocol.
14. For the screening only, 7 days are counted as 7 working days and not calendar days. Non-working days are weekend (Saturday, Sunday) and any country specific public holiday.
15. Endoscopy video/digital image taken prior to ICF signature can be used as index endoscopy for the enrollment, if taken within 7 days of the planned treatment day. For patients invited for screening upper endoscopy based on their past medical history (see Section 5 of protocol), the ICF will be signed prior to the endoscopy. The screening procedures must start with endoscopy and in case the patient doesn't show LA grade C or D erosions, the rest of the screening procedures must not be conducted. This screening endoscopy must be obtained within 7 working days of planned randomization.

Approval Signatures

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Document Number: CCI [redacted]

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Document Approvals	
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Parexel International
Statistical Analysis Modification Requests

Sponsor Project Number: #CX842A2201		**Parexel Project Number: 249403**	
Sponsor Name: Cinclus			
Date of Unblinding: 19 October 2022			

This document has been signed electronically on the final pages by the following:

Signatory	
Author:	PPD Project Role: PPD

Parexel International
Statistical Analysis Modification Requests

Sponsor Project Number: #CX842A2201		**Parexel Project Number: 249403**	
Sponsor Name: Cinclus			
Date of Unblinding: 19 October 2022			

This document has been signed electronically on the final pages by the following:

Signatory	
Author:	PPD Project Role: PPD

Life Science

Statistical Analysis Plan

- amendment 01

Client Study Code:	CX842A2201
Study Title:	Cinclus phase II study
SDS Project Code:	CIN_CX842A2201

Document Control

Control

Document Name	Statistical Analysis Plan Amendment 1
Based on clinical study protocol and amendment versions	Study Protocol, amendment 2.0 (25 February 2022)
Eudract number	2020-003319-91
Version	Version 1.0
Study statistician	PPD SDS Life Science (SDS)
Authors	PPD SDS)
Status	Final

Signatures

Prepared at SDS by:

PPD

History

Version	*Modified By*	*Date*	*Description of Changes*
0.1	PPD	2023-03-03	Only Analysis dataset specification included
0.2		2023-03-07	Subsets and some of the endpoints added
0.3		2023-03-08	Statistics methods complete
0.4		2023-03-16	First version for review within SDS
0.5		2023-03-16	Second version for review within SDS

0.6	PPD	2023-03-17	First complete draft for Cinclus to review
0.7		2023-04-04	Version for SDS internal language review
0.8		2023-04-04	Second complete draft for Cinclus to review
1.0		2023-04-11	Final version (same as previous)

Table of Contents

Abbreviations

Abbreviation	Term
AE	Adverse Event
AESI	Adverse Event of Special Interest
BMI	Body Mass Index
CSPCSP	Clinical Study Protocol
ECGECG	Electrocardiogram
eDiary	Electronic Diary
FAS	Full Analysis Set
FDAFDA	Food and Drug Administration
GERDGERD	Gastro-Esophageal Reflux Disease
H. Pylori	Helicobacter Pylori
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
LA grade	The grade of esophagitis according to the Los Angeles classification system
mFAS erosive	Modified Full Analysis Set erosive
mRESQ-eD	modified Reflux Symptom Questionnaire electronic Diary
PKPK	Pharmacokinetic
PKS	Pharmacokinetic Analysis Set
PRPR	Partial Response
PPI	Proton-pump inhibitor
PPS	Per-Protocol Analysis Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SSSS	Safety Analysis Set
TEAE	Treatment Emergent Adverse Event
QDQD	Once daily (quaque die)
QOLRADQOLRAD	Quality of Life in Reflux and Dyspepsia

1. Introduction

Study CX842A2201 was subject to procedural changes after study start, in accordance with FDA advice. The changes rendered unforeseen consequences which were partly missed in the Statistical Analysis Plan (SAP) signed before unblinding the data of the study. The pre-specified SAP, "249403_SAP_20221013_v1.0.docx", will be referred to as the "original SAP".

The current document is SAP amendment complementary to the original SAP. In this document it is assumed that the original SAP is followed unless otherwise stated, but the text written in this SAP amendment overrides the original SAP.

Section 2 summarizes the study objectives and endpoints. Section 3 gives an overview of the procedural changes to the study, including timelines, problems that arose and solutions implemented. Section 4 (Analysis methods) defines all analysis sets and subgroups, lists all analyses that are to be done for each analysis set and subgroup. The hierarchy of different study results, as a consequence of the procedural changes, is based on whether the analysis was prespecified in the original SAP and/or in the clinical study protocol (CSP), "249403 02.01.02 Protocol 03 Sep 2020 English 1.0 Clean.pdf", or not prespecified. This hierarchy is explained in Section 4.3.3.

2. Study objectives and endpoints

This table is identical to that in the original SAP, except the Healing by local reading has been defined as an exploratory endpoint (bottom line).

Objectives	Endpoints
Primary	
The primary objective of the study is to support dose selection for X842, through assessment of healing of erosive esophagitis due to GERD after 4 weeks of treatment.	Healing of erosive esophagitis due to GERD based on endoscopic assessment after 4 weeks of double-blind treatment.
Secondary	
Evaluate the safety and tolerability of the four dose levels of X842 and lansoprazole, where lansoprazole will serve as the active comparator.	Physical examination, weight, BMI, vital signs, electrocardiogram (ECG) recordings, safety laboratory measurements (hematology/clinical chemistry/urinalysis), adverse event (AE), treatment emergent adverse event (TEAE), adverse event of special interest (AESI), serious adverse event (SAE) reporting, concomitant medication(s).

Objectives	Endpoints
Evaluate the reflux related symptom pattern during the initial 4 weeks treatment with four dose levels of X842 and with lansoprazole, and the symptom pattern during the subsequent additional 4 weeks (Weeks 5-8) open-label treatment with lansoprazole 30 mg QD.	• Percentage of heartburn-free 24-hour days during the Weeks 1-8 (Visits 2-9) based on eDiary (mRESQ-eD), including splits into day- and nighttime evaluations • Percentage of 24-hour days with at most mild heartburn symptoms during the Weeks 1-8 (Visits 2-9) based on eDiary (mRESQ-eD), including splits into day- and nighttime evaluations • Investigator assessment of symptom at Weeks 1-8 (Visits 2-9) • Reflux related impact as measured by change from baseline in QOLRAD scores assessed after 1, 2, 4 and 8 weeks of treatment.
Exploratory	
CCI [redacted]	

3. Background and timelines of unforeseen study events

This SAP amendment is written after the unblinding of study data, as motivated by some unforeseen events that occurred after the study start, and for which solutions were only partially captured in the original SAP. The sequence of events is summarized in

Abbreviations: CSP = Clinical Study Protocol, FDA = Food and Drug Administration, FAS = Full Analysis Set, FAS erosive = Full Analysis Set erosive, FAS erosive PR = Full Analysis Set erosive Partial Responders, mFAS erosive = modified Full Analysis Set erosive, SAP = Statistical Analysis Plan. # and *: References between panels describing the same issue. and below.

A change in study proceedings was committed after study start according to advice from FDA. It was agreed that instead of letting the assessments of LA grade of erosive esophagitis due to GERD rely on the judgement of the local investigator at the clinic at the time of endoscopy, images taken at the endoscopy were to be sent for a central review, and these central readings were to define the LA grade of patients in the study.

LA grades A, B, C and D represent increasing severity of erosiveness, and non-erosive patients are classified with LA grade 0 (zero). The LA grades define both the patients' level of disease at Baseline (grade A, B, C or D), and the primary efficacy endpoint healing of erosive esophagitis after 4 weeks of treatment (grade 0 corresponds to "healed", and grade A, B, C or D corresponds to "not healed").

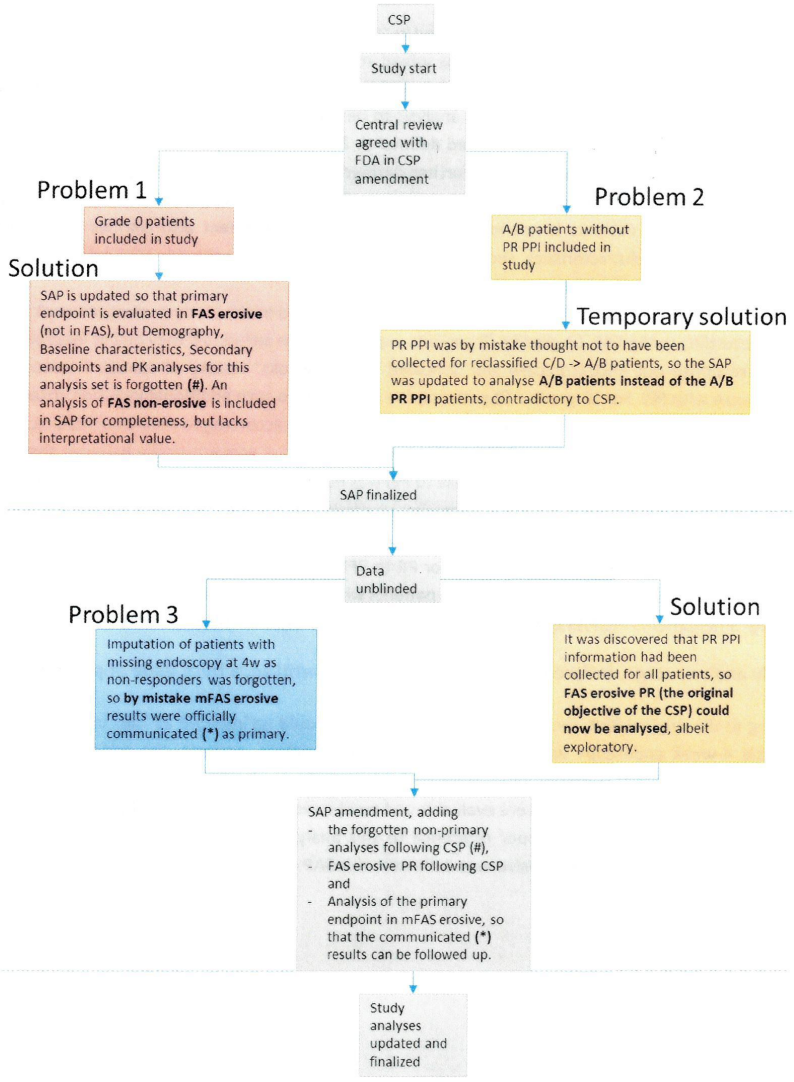
Each patient was therefore included in the study based on local assessments, however, was later re-classified by central readings. This gave 2 immediate consequences, which are adhered to in this SAP amendment:

1. Non-erosive patients were included in the study and in the FAS (the analysis set intended for the primary analysis) in disagreement with the CSP. This was solved in the original SAP by the creation of 2 subsets of FAS, including **FAS erosive** and **FAS non-erosive**, and specifying that the primary endpoint would be performed in both (implying the FAS erosive analysis to be the primary analysis of the study.). In this SAP amendment, these 2 subsets were instead defined as 2 separate analysis sets, to make subgroup analyses within them easier to describe. It is further clarified explicitly that the primary objective of the study will be assessed in FAS erosive, and analyses on the FAS non-erosive are seen as exploratory, as healing in non-erosive patients is not interpretable. This SAP amendment also clarifies to present demography, baseline characteristics, secondary, sensitivity and pharmacokinetic (PK) results for the FAS erosive, which were missed in the original SAP.
2. LA grade A/B patients without a history of PR to PPI were included in the study in disagreement with the CSP. According to the CSP, LA grade A/B patients were only to be included if they had at least partial symptom response but endoscopically still unhealed after 8 weeks' history of standard treatment healing course with PPI. For LA grade C/D patients, the study has no such additional inclusion criterion. Some patients entered the study classified as LA grade C/D patients according to their local reading, and were re-classified as LA grade A/B patients in the central reading. It was erratically believed that for these patients, information about prior response to PPI was never collected. For this reason, the original SAP was hastily adjusted so that instead of assessing LA grade A/B patients with prior PR to PPI and LA grade C/D patients, assessments would be done on LA grade A/B patients and LA grade C/D patients. After data unlock it was discovered that the prior PR to PPI information had in fact been collected for all patients, so it is hence possible to identify the patients which reflect the primary objective of the CSP. In this SAP amendment, the **FAS erosive PR** has been defined to capture this population.

During the study analysis stage, before this SAP amendment was written, a third issue appeared:

3. According to the original SAP, the primary endpoint healing should be imputed as "no" in patients for whom the 4-week endoscopy was never done. This was forgotten. Instead, the patients with no evaluation of the primary endpoint were dropped from analysis, so that healing results based on the subset of FAS erosive patients, who were evaluable at 4 weeks, were communicated officially as primary results of the study. To enable proper reference to this analysis in follow-up communication, the corresponding analysis set **mFAS erosive** was defined in this SAP amendment.

Figure 1.3-2. Flow chart to summarize the background reasons and timelines for decisions and changes regarding the analysis of the study data



*Abbreviations: CSP = Clinical Study Protocol, FDA = Food and Drug Administration, FAS = Full Analysis Set, FAS erosive = Full Analysis Set erosive, FAS erosive PR = Full Analysis Set erosive Partial Responders, mFAS erosive = modified Full Analysis Set erosive, SAP = Statistical Analysis Plan. # and *: References between panels describing the same issue.*

All study analysis sets are defined in Section 4.3. The issues and their solutions, as well as timelines, renders a hierarchy of how different results from the different analysis sets are interpreted. This is specified in Section 4.3.3.

4. Analysis Methods

4.1 General presentation considerations

Summary tables of continuous and categorial variables will contain the number of patients with missing values.

4.2 Study patients

4.2.1 Protocol deviations

As described in the original SAP, failure to meet inclusion or exclusion criteria will be classified as a major protocol deviation, and hence LA grade A/B patients who fail to meet the following inclusion criteria will be posted with a major protocol deviation:

- have at least partial symptom response but endoscopically still unhealed after 8 weeks history of standard treatment healing course with PPI.

The study contains patients reclassified as LA grade A/B patients in the central reading which were not classified as A/B patients by the local reading and fail to meet the above inclusion criterion. This will be classified as a separate protocol deviation.

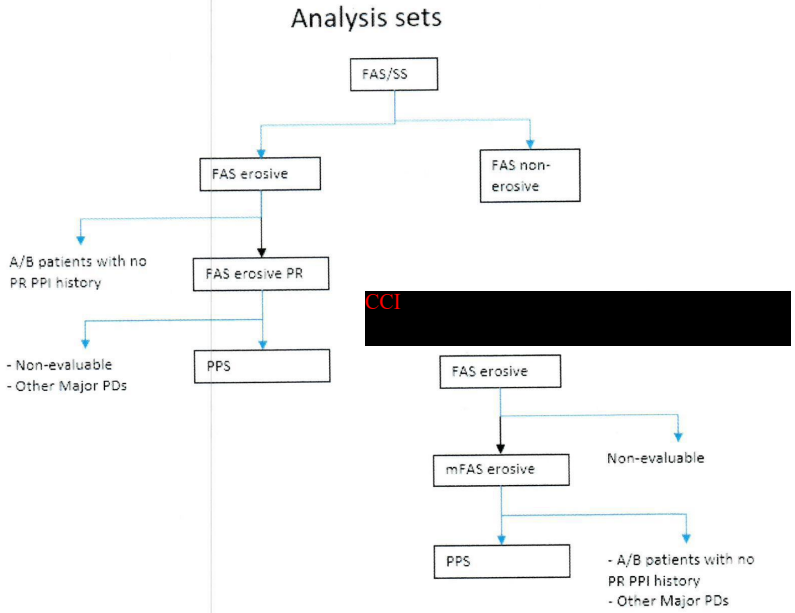
- No history of partial response to PPI

4.3 Analysis data sets

The study analysis sets are defined in sections below, and graphically described in flowcharts in

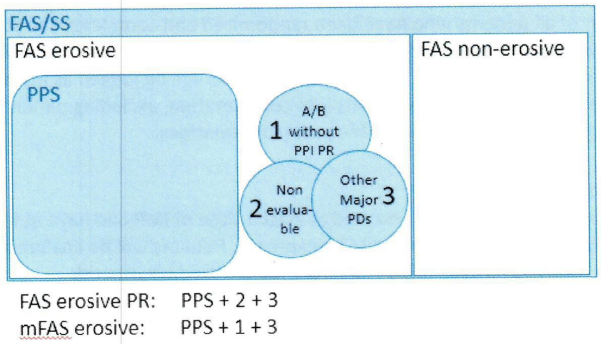
Figure 34-4 and in a Venn diagram in Figure 5.4-6.

Figure 34-4. Flowchart of study analysis sets (excluding "Enrolled" and "Randomized")



Abbreviations: FAS = Full Analysis Set, FAS erosive = Full Analysis Set erosive, FAS erosive PR = Full Analysis Set erosive Partial Responders, mFAS erosive = modified Full Analysis Set erosive, PPI = Proteon Pump Inhibitor, PD = Protocol Deviation.

Figure 5.4-6. Venn diagram of study analysis sets (excluding "Enrolled" and "Randomized")



Note that 1 contains only A/B patients (no C/D patients). Hence, for the subgroup of C/D patients, FAS erosive PR is identical to FAS erosive.

Abbreviations: FAS = Full Analysis Set, FAS erosive = Full Analysis Set erosive, FAS erosive PR = Full Analysis Set Partial Responders, mFAS erosive = Modified Full Analysis Set erosive, PD = Protocol deviation, PPI = Proton pump inhibitor, PPS = Per Protocol Set, SS = Safety Set.

4.3.1 Analysis Data Sets following the original SAP

The following analysis sets were defined prior to unblinding of the study data. However, in the original SAP, the FAS erosive and FAS non-erosive were defined as subsets of FAS. In this SAP amendment, they are instead defined as analysis sets, but that does not inflict on the status of FAS erosive analyses being the primary analyses of the study.

4.3.1.1 Enrolled

All patients who signed the ICF (including screening failures).

4.3.1.2 Randomized

All patients who have been randomized.

4.3.1.3 Safety Analysis Set, SS

The safety analysis set SS will consist of all patients who have been randomized and received at least 1 dose of IMP. Patients will be analyzed according to the treatment actually received (in case this differs from randomized treatment).

4.3.1.4 Full Analysis Set, FAS

The FAS will consist of all patients who have been randomized and received at least 1 dose of IMP. Patients will be analyzed according to randomized treatment (any randomized but not treated patient will be marked and reported as such).

4.3.1.5 Full Analysis Set erosive, FAS erosive

The FAS erosive is a subset of FAS and consists of patients who have also fulfilled the following:

- Classified as erosive (Grade A, B, C or D) at screening according to the central reading or imputed by local reading if missing.

4.3.1.6 Full Analysis Set erosive, FAS non-erosive

The FAS non-erosive is a subset of FAS and consists of patients who have also fulfilled the following:

- Classified as non-erosive (Grade 0) at screening according to the central reading or imputed by local reading if missing.

4.3.1.7 Per-Protocol Analysis Set, PPS

The PPS will consist of all patients who have been randomized and completed the study without any major protocol deviations that are judged to compromise the analysis of the data. Mis-randomized patients will be removed from the PPS. All protocol violations will be judged as major or minor, taking composite effects of protocol deviations into consideration, excluding patients for whom the clinical outcome is qualitatively affected by the protocol deviations.

4.3.1.8 PK Analysis Set, PKS

The PKS will consist of all patients who received at least 1 dose of IMP and have at least 1 measurement of plasma concentration of X842/linaprazan. Patients will be analyzed according to the treatment actually received (in case this differs from randomized treatment).

4.3.2 Exploratory Analysis Data Sets

CCI [redacted]

CCI

[redacted]

4.3.3 *Hierarchy of analysis sets and results*

Due to the unforeseen events and their timelines described in Section 3, the study results will formally follow a hierarchy with 3 levels.

Level 1 results are the results that agree with the original SAP:

- Results on FAS, FAS erosive and PPS.
- The FAS erosive healing results are the primary results of the study.

Level 2 results are the results that agree with the CSP and/or were clearly missed in the original SAP:

- Demography, baseline characteristics, secondary endpoints and sensitivity analyses on FAS erosive and dose – response models on subgroups A/B and C/D on PPS. All of these results were clearly missed in the original SAP, given that FAS erosive healing was declared to be the primary analysis.
- All analysis on FAS erosive PR. This analysis set corresponds to the originally intended patient population as per CSP, and gives the results of highest interest of this study, albeit based on fewer patients than originally planned.

CCI

[redacted]

Both Level 2 and Level 3 results are formally explorative, as they were not defined in the original SAP. Note, however, that no re-classification of patient protocol deviations which would have altered the assignment of analysis sets were done after the data unlock. Hence that data integrity is kept high in particular in the Level 2 FAS erosive PR results, which captures the population of the primary objective according to CSP.

4.3.4 *Subgroups*

Subgroup analyses will be performed for uniformity of the primary endpoint, for Healing by local reading and for the two secondary efficacy endpoints

- Percentage of heartburn-free 24-hour days during the Weeks 1-8 based on eDiary (mRESQ-eD) and
- Percentage of 24-hour days with at most mild heartburn symptoms during the Weeks 1-8 based on eDiary (mRESQ-eD),

on the following subgroups:

1. Erosive esophagitis due to GERD LA grade (A/B, C/D)
2. Age (<60 years, ≥60 years)
3. Sex (Male, Female)
4. Center (Centers with less than 20 patients will be pooled into "Other")
5. Subgroups by H. Pylori status at baseline
6. Central reading of LA grade imputation status (imputed, not imputed) (Patients for whom the endpoint Healing has been imputed by local healing at either Baseline or at Visit 5, versus patients for whom a central reading of Healing has been used at both Baseline and Visit 5.)
7. Reclassification subgroups:
    - Grade C/D that stayed C/D
    - Grade C/D reclassified as A/B
    - Grade C/D reclassified as grade 0 (non-erosive)
    - Grade C/D reclassified as missing
    - Grade A/B reclassified as C/D
    - Grade A/B that stayed A/B
    - Grade A/B reclassified as grade 0 (non-erosive)
    - Grade A/B reclassified as missing
8. History of PPI treatment (yes/no) in A/B patients

4.4 Disposition and Background information data

The disposition of patients will be presented.

A summary of the number and percentage of patients in the FAS, FAS erosive, mFAS erosive, FAS erosive PR, FAS non-erosive, PPS, SS and PKS by study treatment group and overall and the reason for exclusion from an analysis set (if applicable) will be provided for the Randomized Set. Listings will be provided.

Demographic and baseline characteristics will be summarized for the FAS and SS as pre-specified in the original SAP.

Demographic and baseline characteristics will also be summarized for the FAS erosive, FAS erosive PR and PPS (not pre-specified in the original SAP).

Medical/surgical history summaries will be provided on the FAS, FAS erosive and FAS erosive PR. Listings will be provided.

Prior and concomitant Medications and prior PPI Treatment will be provided on the FAS, FAS erosive and FAS erosive PR. Listings will be provided.

Treatment exposure will be summarized on the SS.

Compliance will be summarized on the FAS, FAS erosive and FAS erosive PR.

4.5 *Efficacy Analyses*

4.5.1 Analysis and data conventions

4.5.1.1 Adjustment for covariates

The primary efficacy dose – response model analysis will be adjusted for the following baseline covariates, where the second covariate is modified compared to the original SAP.

1. Center
2. Erosive esophagitis due to GERD LA grade C/D, erosive esophagitis due to GERD LA grade A/B ~~who are partial responders to PPI treatment.~~

The modification is an adjustment to the included LA grade A/B patients without history of partial response to PPI treatment. In analysis datasets FAS erosive PR and PPS, patients who are not partial responders to PPI treatment are not included, and hence the covariate adjustment will effectively follow the original SAP and the original intention of the objective.

4.5.2 Primary Efficacy Analysis

The primary endpoint Healing will be analysed for the FAS erosive as primary analysis.

Healing will also be analysed for the PPS, as a supportive analysis.

See also subgroup analyses listed in Section 4.5.5 and sensitivity analyses listed in Section 4.5.6.

4.5.3 Secondary Efficacy Analyses

All secondary efficacy endpoints will be analysed for the FAS.

All secondary efficacy endpoints will also be analysed for the PPS.

See also subgroup analyses listed in Section 4.5.5.2.

All secondary safety analyses will be presented on SS.

4.5.4 Exploratory Efficacy Analyses

CCI

[redacted]

4.5.5 *Subgroup Analyses*

All planned subgroup analyses are listed in this section, which overrides the corresponding sections in the original SAP.

CCI [redacted]

4.5.5.1 Subgroup analyses for the primary efficacy endpoint Healing

The primary efficacy endpoint Healing will be summarized by treatment group and in total for the following subgroups and in the following analysis sets:

Subgroups	*Analysis sets*	*Comment*
Erosive esophagitis due to GERD LA grade (A/B, C/D)	FAS erosive, FAS erosive PR, mFAS erosive, PPS	
Age (<60 years, ≥60 years)	FAS erosive, FAS erosive PR, PPS	
Sex (Male, Female)	FAS erosive, FAS erosive PR, PPS	
Center (Centers with less than 20 patients will be pooled into "Other")	FAS erosive, FAS erosive PR, PPS	
Subgroups by H. Pylori status at baseline	FAS erosive, FAS erosive PR, FAS non-erosive, PPS	
CCI [redacted]		
Reclassification subgroups	FAS	Sensitivity analysis
History of PPI treatment (yes/no) in A/B patients	FAS	

For the subgroups by LA grade (A/B and C/D), Healing percentages will also be presented in bar charts for FAS erosive and PPS.

The primary efficacy endpoint Healing will be assessed in dose – response models in the following subgroups and in the following analysis sets:

Subgroups	*Analysis sets*	*Comment*
CCI [redacted]		

4.5.5.2 Subgroup analyses for two secondary efficacy endpoints

The following two secondary efficacy endpoints

- Percentage of heartburn-free 24-hour days during the Weeks 1-8 based on eDiary (mRESQ-eD) and
- Percentage of 24-hour days with at most mild heartburn symptoms during the Weeks 1-8 based on eDiary (mRESQ-eD)

will be summarized by treatment group and in total for the following subgroups and in the following analysis sets:

Subgroups	*Analysis sets*	*Comment*
Erosive esophagitis due to GERD LA grade (A/B, C/D)	FAS erosive, FAS erosive PR	
Age (<60 years, ≥60 years)	FAS erosive, FAS erosive PR	
Sex (Male, Female)	FAS erosive, FAS erosive PR	
Center (Centers with less than 20 patients will be pooled into "Other")	FAS erosive, FAS erosive PR	

4.5.5.3 Subgroup analyses for Healing by local reading

The exploratory efficacy endpoint Healing by local reading will be summarized by treatment group and in total in the following subgroups and in the following analysis sets:

Subgroups	*Analysis sets*	*Comment*
Erosive esophagitis due to GERD LA grade (A/B, C/D)	FAS	Sensitivity analysis
Reclassification subgroups	FAS	Sensitivity analysis

4.5.6 Sensitivity Analyses

In the FAS, the following sensitivity analyses will be done to assess the stability of the primary endpoint Healing analyses:

1. The primary endpoint Healing will be summarized by treatment group and in total in reclassification subgroups.

CCI [redacted]

In the FAS erosive and the FAS erosive PR, the following sensitivity analyses will be done to assess the stability of the primary endpoint Healing analyses (same as 2 above):

- CCI [redacted]

If there are more than 5% of patients with missing healing results, a tipping point method sensitivity analysis will also be performed with respect to the non-response imputation of missing values. Scenarios assuming probability of response 20%, 40%, 60%, 80% and 99% will be simulated. Fifty datasets for each probability will be generated, and for each one, an analysis will be conducted, Rubin rules will be used to combine the results.

5. References

1. Original SAP 249403_SAP_20221013_v1.0.docx
2. Clinical Study Protocol 249403 02.01.02 Protocol 03 Sep 2020 English 1.0 Clean.pdf.
3. Clinical Study Protocol amendment 249403 Cinclus_CX842A2201 Protocol_Amendment 2_final_25 Feb 2022.pdf.
4. Statistical Principles for Clinical Trials (ICH Topic E 9). EMEA. September 1998, CPMP/ICH/363/96.